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REVIEW

Incentive salience: novel treatment strategies for major depression

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This article proposes that a recent shift in our understanding of dopamine function may support translational research to target deficits in positive emotions and reward processing in individuals with major depressive disorder (MDD). We review how dopamine functions to modulate approach behaviors in response to positive incentives, and we describe the incentive salience hypothesis, which posits that dopamine primarily modulates "wanting," or anticipatory reward, rather than "liking," or subjective pleasure. Although the incentive salience hypothesis was first proposed to help explain how drugs of abuse may reinforce harmful behaviors in the absence of continued pleasure or "liking," it may also provide a basis for understanding and developing new treatment approaches for MDD. Specifically, it provides a rationale for combining behaviorally activating psychotherapies and pro-dopaminergic agents to target impaired reward processing in MDD.

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Introduction

Advances in the pharmacological treatment of major depression have often been the result of serendipity. Imipramine was first observed to have mood effects in a pilot study testing the molecule, G 22355, an analog of chlorpromazine, as an antipsychotic. In a perhaps apocryphal story, Roland Kuhn, a principle investigator for the study, was impressed by the molecule's mood elevating properties, after a patient with schizophrenia absconded from a large, state hospital in Switzerland, and was found singing elatedly, as he bicycled through the streets of the surrounding town.[1] Similarly, the impetus for studying monoamine oxidase inhibitors (MAOIs) as antidepressants can be traced to observations of patients with tuberculosis evincing more positive emotions when taking the antibiotic, iproniziad. Morris Solotorovsky, then Head of Bacteriology at the Merck Institute and an expert on the tuberculosis, quipped "but they are dancing with holes in their lungs."[2]

Since the discovery of antidepressants affecting monoamine systems in the 1950s and 1960s, pharmacological advances have been fewer and the rate of antidepressant development has slowed.[3] This may reflect the rise in placebo response[4]; the systemic limitations of large, multisite trials[5]; the difficulty of generating rational hypotheses for drug development, given our incomplete understanding of the neural processes underlying emotions, cognitions, and behaviors; and the *phenotype problem*, defined here as the inclusion of heterogeneous samples in antidepressant trials, likely dampening signal detection.

As we learn more about the biology of neural networks and signaling cascades, as well as processes of synaptic plasticity and environmental transduction, there is a greater need for research, which moves us from insights into neural mechanisms toward innovative treatment strategies. Modern pharmacotherapies for depression have not produced significant gains in efficacy. For example, in trials with selective serotonin reuptake inhibitors (SSRIs), approximately 29–46% of depressed patients fail to respond or achieve only partial response,[6] between 40% and 60% of responders will relapse within one year,[7,8] and rates of remission have been estimated to be about 37%.[9]

This article proposes that a recent shift in our understanding of dopamine function may support translational research to improve care for individuals with major depressive disorder (MDD). We will briefly review how dopamine functions to modulate approach behaviors in response to positive incentives; discuss the *incentive salience hypothesis* of dopamine function and its potential relevance to MDD; and explore a translational treatment approach, which combines behavioral

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activation therapy and pro-dopaminergic medications to target the incentive processing and associative learning of reward.

The Role of Dopamine in Reward

Dopamine in healthy subjects

Historically, the use of dopaminergic stimulants can be traced to their performance-enhancing effects in military personnel during World War II.[10] Consistent with these initial empirical observations, Taneja *et al.*[11] found that healthy subjects randomized to treatment with the pro-dopaminergic agent, modafinil, reported significantly increased positive emotionality—a dimensional construct that includes positive arousal, motivation, and hedonic components—compared to controls. Recent neuroimaging findings also indicate that dopaminergic processes modulate motivational drives and approach behaviors in response to positive incentives.[12,13] For example, radioligand-based positron-emission tomographic (PET) studies have found increased metabolic activity within the ventral striatum following exposure to rewarding stimuli, including music and monetary gains,[14–16] and amphetamine-induced increased release of dopamine in the ventral striatum has been linked to increased energy, arousal, and positive emotionality.[17]

Dopamine in MDD

There is now strong evidence that the pathophysiology of depression involves abnormal functioning of cortico-basal ganglia reward circuitry, which is highly innervated by dopaminergic projections from the midbrain and may be targeted by pro-dopaminergic medications. Findings of dopamine dysregulation in MDD populations include reduced concentrations of the dopamine metabolite homovanillic acid (HVA) in cerebrospinal fluid,[18,19] reduced L-dopa uptake across the blood–brain barrier,[20] reduced density of striatal dopamine transporters,[21] and increased striatal binding to D2/D3 receptors,[22,23] with several conflicting studies also reported.[24,25]

Additionally, in rodent models, depressive phenotypes have been linked to the dysregulation of dopaminergic transmission through the ventral tegmental area (VTA) and nucleus accumbens (NAcc) under stress conditions.[26,27] Acutely, upregulation of this pathway may promote adaptive arousal; however, chronic desensitization, overstimulation of cAMP binding protein (CREB), and abnormal expression of BDNF and the protein kinase AKT in the ventral striatum are associated with increased immobility times on the forced swim test.[26] Abnormal expression of circadian rhythm-modulating genes, such as CLOCK and DAT, distributed throughout the reward circuit, and concentrated in the NAcc, are associated with MDD-like behaviors, while CLOCK and DAT-knockdown mutant mice demonstrate increased positive arousal, motivation, and incentive processing.[28]

Dopaminergic treatments for MDD

Stimulants have a promising mechanism of action by altering dopamine (DA) kinetics in the ventral striatum (VS) and prefrontal cortex (PFC). As a class, they also have historical importance in the treatment of MDD. There have been five positive open-label augmentation trials using stimulants with MAOIs or TCAs for refractory depression.[29] Two recent studies on adding stimulants to SSRIs showed improvement for specific symptoms of fatigue and apathy.[30,31] However, controlled studies have failed to demonstrate significant changes in response or remission.[32]

In contrast, dopamine antagonists, such as Seroquel and Zyprexa, and the mixed agonist-antagonist Abilify, have stronger evidence bases for MDD. Though it is plausible that individuals with biologically heterogeneous forms of depression could respond differentially to stimulants and antipsychotics, there remains a striking discrepancy between basic science research supporting the hypothesis that stimulants have therapeutic properties, specifically targeting motivational drives and approach behaviors impaired in MDD, and the paucity of controlled trials demonstrating antidepressant effects. However, recent findings of studies conducted in animals (see below) may provide a viable explanation for this discrepancy and a rationale for revisiting the use of stimulants in the treatment of MDD.

Incentive Salience Hypothesis

Dopamine deconstructed

Dopamine has been viewed as a candidate "pleasure neurotransmitter" for over 30 years.[33] Yet data from animal studies of the NAcc and ventral pallidum (VP) suggest that, rather than impacting the experience of pleasure or hedonic processing, dopamine has its greatest effects on two types of reward processing—incentive salience and reward learning.[34,35] Microinjection of amphetamine (AMPH), an indirect dopamine agonist, into the NAcc shell in rodents has been shown to increase the incentive impact of reward cues (the degree to which they elicit "wanting" or their "incentive salience"), as well as secondary reinforcement when response reinforcement contingencies exist (reward learning), without enhancing the hedonic impact of rewards ("liking") (see Figure 1).[36–38] Using event-related MRI and a monetary incentive delay paradigm, Knutson *et al.*[39] found related evidence that

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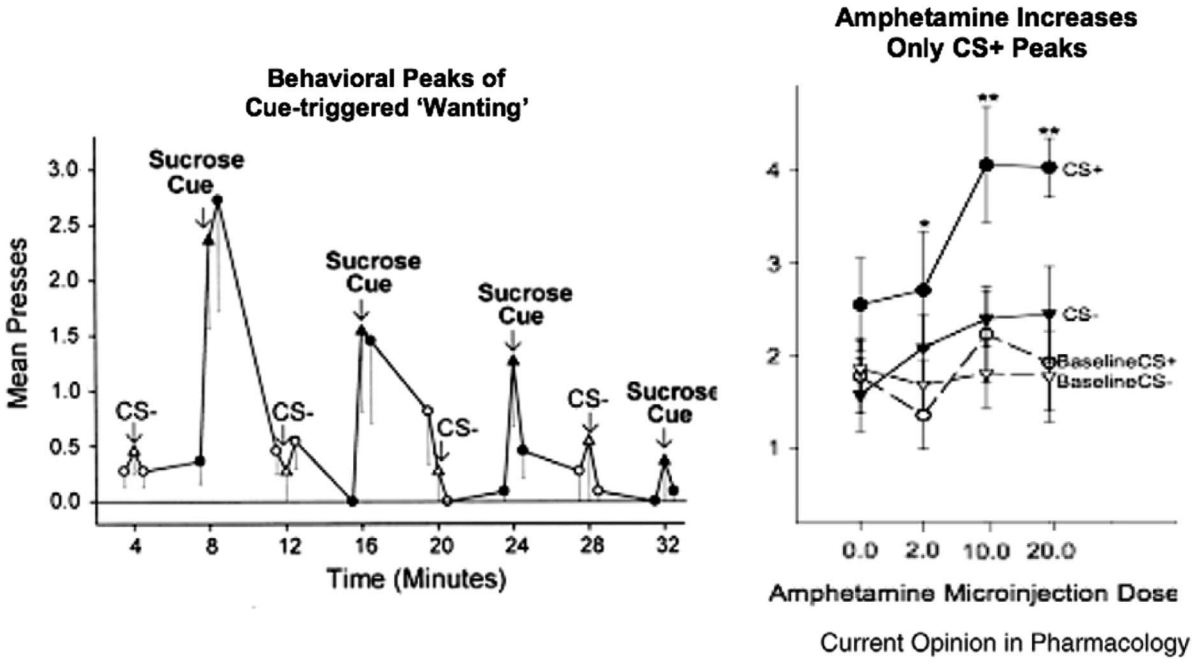

Figure 1. NAc amphetamine amplification of cue-triggered "wanting." Transient peaks of "wanting" for sucrose reward are triggered by 30-s appearances of a Pavlovian sucrose cue in a Pavlovian-Instrumental Transfer test (CS+; right). Amphetamine microinjection in nucleus accumbens magnifies "wanting" for sugar reward—only in the presence of the reward cue (CS+), indicating magnification of the cue's incentive salience. Only cue-triggered "wanting" was enhanced by this dopamine-related stimulation. By contrast, "liking" reactions to sucrose were not amplified by amphetamine microinjections in NAc (not shown). Drug-induced sensitization of NAc-related systems produces a similar pattern of effects that lasts much longer. Reprinted from Current Opinion in Pharmacology, Volume 9, Berridge, KC, Robinson, TE & Aldridge, JW. Dissecting components of reward: 'liking', 'wanting', and learning, 65–73 (2009), with permission from Elsevier.

AMPH modulates both psychological and physiological aspects of incentive processing in humans. Healthy subjects receiving AMPH demonstrated increased positive arousal for anticipating gain and avoiding loss, as measured by increased cue-related excitement and changes in ventral striatum (VS) activity. Additionally, AMPH subjects displayed increased right NAcc activation during loss anticipation, prompting the investigators to conclude that AMPH treatment "may also promote tonic VS activity during anticipation of loss, which might facilitate increased positive arousal and concomitant affective reframing of potential loss as potential gain."

Incentive salience

The incentive salience hypothesis proposes that dopamine has greater effects on "wanting," or incentive salience, than on "liking," or hedonic processes. "Incentive" is defined as the amount of work an organism will do in relation to the reward value of the stimulus. "Salience" is defined as how attractive a given stimulus is to an organism.

This hypothesis was pioneered by the neuroscientists Kent Berridge and Terry Robinson, who were intrigued by the possibility of understanding the neural mechanisms of "wanting" and "liking."[41] They began by characterizing phenotypic expressions of "liking" and "disliking" in rodent models, which could be elicited by contact with rewarding or aversive stimuli, such as sweet or bitter tastes (see Figure 2). They then stimulated specific reward-mediating pathways via microinjection of neurochemicals, such as dopamine and the μ opioid agonist [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO), into the limbic forebrain, and measured amplification or abrogation of liking reactions. Contrary to the hedonia hypothesis, first articulated by Wise, as, "The dopamine junctions represent a synaptic way station … where sensory inputs are translated into the hedonic messages we experience as pleasure, euphoria or 'yumminess,'"[40] (p. 94) they found that activation of the mesolimbic DA system was neither necessary nor sufficient for altering the hedonic impact of a stimulus, ie, for mediating "liking."[41]

Additionally, genetically engineered hyperdopaminergic mutant mice, lacking the gene transporter for dopamine reuptake, demonstrate significant amplification of "wanting" (measured by 3 different tests of incentive motivation) but not "liking" in response to sucrose rewards.[41,42] Elegant research performed by

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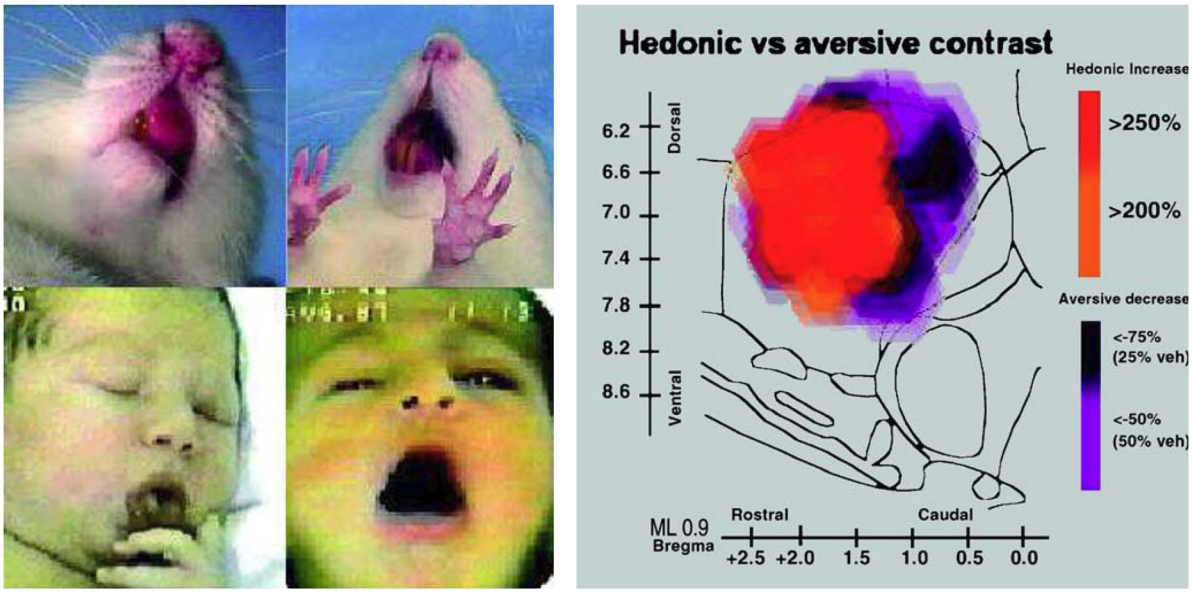

Figure 2. "Liking" reactions and brain hedonic hotspots. Far left: Positive hedonic "liking" reactions are elicited by sucrose taste from human infant and adult rat (eg, rhythmic tongue protrusion). By contrast, negative aversive "disliking" reactions are elicited by bitter quinine taste (center left; see online video). From Steiner *et al.*, 2001. Right: Opioid hedonic hotspot in medial shell of nucleus accumbens where μ opioid agonist DAMGO causes increases in the number of "liking" reactions elicited by sucrose taste (red). Purple shows where opioid activation suppresses "liking" and "disliking" reactions elicited by quinine. Dopamine lacks any identified yellow hedonic hotspot and possesses only suppression regions (purple equivalents) as far as is known. Permission to reproduce this figure from Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl). 2007;191(3):391–431, was given with kind permission from Springer Science and Business Media.

Salamone *et al.*[43] has also demonstrated that antagonism of dopamine in the NAcc specifically impairs activational aspects of motivation affecting rodent feeding behaviors, which may parallel, phenomenologically, the depressive symptoms of anergia, psychomotor slowing, and behavioral isolation. Finally, in rodent models, neurochemical lesioning of ascending DA projections through the medial forebrain did not suppress the hedonic impact of rewards, even with the loss of approximately 99% of DA neurons in both the NAcc and neostriatum.[44]

The failure of pro-dopaminergic signaling to elicit increased liking reactions contrasts with the effects of other specific neurotransmitter systems, including opioids and cannabinoids, which do change the hedonic impact of various stimuli. For example, microinjection of these neurotransmitters or their agonists into circumscribed portions of limbic structures such as the medial shell of the nucleus accumbens or the posterior portion of the ventral pallidum can double or triple the number of "liking" reactions elicited by sucrose taste.[45,46] In dynamic models of neural connectivity, these "hedonic hotspots" form circuits connecting multiple brainstem and forebrain regions, described by Berridge *et al.* as "akin to multiple islands of an archipelago that trade together."[38]

Relevance to human reward processing

These findings have now been extended to humans by examining the behavioral and neural correlates of dopamine neurotransmission in Parkinson's patients with dopamine dysregulation syndrome and in healthy volunteers. For example, Volkow *et al.*[47] and colleagues found that individual variation in dopamine receptor occupancy in the striatum was associated with "nonhedonic" ratings of food desire (ie, greater receptor occupancy was linked to a greater incentive impact of food), leading to the conclusion that "the present data are consistent with the notion that dopamine increases the incentive salience of a conditioned cue (e.g., the sight, smell, and taste of food), causing the cue to increase the motivational state of 'wanting' for the reward without necessarily enhancing its hedonic properties" (p. 179). To map the neural processes of wanting and liking in humans, Brian Knutson at Stanford has developed a unique instrument, the monetary incentive delay (MID), which separates anticipatory reward processing ("wanting") and consummatory reward processing ("liking") through a blocked fMRI paradigm.[48] Subjects are shown cues signifying reward, loss, or neutral conditions. This initial anticipatory phase is followed by a timed

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task requiring subjects to click on an electronic target flashed across their computer screens. In a third phase, subjects receive feedback for their performance as actual money gained, lost, or maintained. This work has shown that "wanting" and "liking" are linked with differential activation of distinct regions of the cortical-basal ganglia circuit. In healthy individuals, anticipatory reward appears to recruit the ventral striatum, including the NAcc, VTA, and orbital frontal cortex (OFC), while consummatory reward processing leads to activation of the OFC, medial prefrontal cortex (mPFC), and putamen.[49]

Novel treatment strategies

Although the incentive salience hypothesis was first proposed to help explain how drugs of abuse may reinforce harmful behaviors in the absence of continued pleasure or "liking," it may also provide a basis for understanding and developing new treatment approaches for MDD. Specifically, it may provide a rationale for combining behaviorally activating psychotherapies and pro-dopaminergic agents to target impaired reward processing in MDD, as well as provide an explanatory model for why randomized, controlled trials of stimulants have failed to demonstrate separation from placebo.[32] In healthy individuals, "wanting" and "liking" appear to be tightly linked during every day social interactions and goal-directed activity. In contrast, many patients with MDD are socially withdrawn and disconnected from natural contact with rewards. If pro-dopaminergic agents have greater effects on "wanting" than "liking," as hypothesized by the incentive salience model, when depressed individuals are given a stimulant in the absence of concurrent behavioral change, the expected therapeutic benefits would be minimal. Similar to an injured athlete, who is guided through rehabilitation by an athletic trainer, patients with MDD may need a cognitive behavioral therapist (CBT) to help recondition adaptive social and reward rhythms for stimulants to have true antidepressant effects.

There are several evidence-based psychotherapies for depression, including behavioral activation (BA) therapy, self-system therapy (SST), and well-being therapy (WBT), which help patients to increase contact with natural rewards and decrease reward-interfering cognitive distortions. BA is a component form of CBT; its premise is that behavioral change drives mood change and, ultimately, recovery from depression. The BA therapist initially works with the patient to identify context-dependent rewards, and then shapes behavioral change through an ideographically determined schedule of pleasant and rewarding activities.[50] SST fosters an understanding of depression as stemming from failures of goal-pursuit, and targets self-appraisal and regulatory mechanisms related to hedonic and motivational deficits.[51] WBT integrates hedonic and eudaimonic approaches to increase well-being and has been demonstrated to be effective for the treatment of the residual phase of affective disorders.[52] For a more comprehensive review of evidence-based psychotherapies targeting specific aspects of reward-processing and positive emotional regulation, please see Carl *et al.*[53]

Based on the incentive salience hypothesis of dopamine function, we suggest that a combination of treatment with a stimulant and behaviorally activating psychotherapy could have a synergistic effect. The stimulant could facilitate the function of the mesocortical and mesostriatal pathways that are involved in motivated, approach-oriented behavior and the initiation of action ("wanting"), increasing the likelihood that the patient will engage in these approach-oriented psychotherapies and their recommended activities. This facilitated participation by the patient would then lead to exposure to potentially rewarding experiences. Dynamic interactions between the "wanting" and "liking" pathways[38] could also lead to the increased subjective experience of pleasure during these activities. Although additional work will be needed to test this model, the empirical evidence for the success of these types of psychotherapies, integrated with new insights into the organization of reward processing circuitry described above, provides a compelling rationale for this type of combined treatment, particularly in patients with prominent anergic features.

Conclusion

Based on the incentive salience hypothesis, we propose that stimulants may be rediscovered as effective antidepressants, if they are combined with psychotherapies that provide adaptive behavioral and environmental substrates for their neural effects. Proof-of-concept studies may help to test for specific and/or synergistic effects on incentive processing. The strongest initial design may be prospective identification, selecting for MDD patients with residual anhedonic deficits, and then randomizing to combined stimulant and psychotherapy treatment versus psychotherapy alone. Similar to augmentation studies with D-cycloserine,[54] studies examining the therapeutic and neural mechanisms of combined interventions for MDD could support a new paradigm for treating the debilitating deficits in motivation and reward processing experienced by many patients with MDD.

Disclosures

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